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(54) **Pharmaceutical compositions containing calcitonin.**

(57) Pharmaceutical compositions for the intra-nasal administration of calcitonin, characterized by the presence of N-substituted aminoacids, are disclosed.

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PHARMACEUTICAL COMPOSITIONS CONTAINING CALCITONIN

The present invention concerns pharmaceutical compositions containing as active principle a calcitonin peptide.

Nowadays calcitonin are widely used for the treatment of Paget's disease, hypercalcemia and osteoporosis.

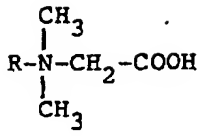
A disadvantageous feature of calcitonins, limiting the field of applications thereof, consists in their long-chain polypeptidic structure making them easily liable to degradation, in unsuited preservation or administration conditions. In addition, calcitonins must be preserved from the contamination by bacteria or other organisms or substances present in the environment as well as in the nasal mucosa, when the intranasal administration is used.

There is therefore the need of pharmaceutical compositions containing calcitonin which are stable and which may easily prevent the contamination by microorganisms and enzymes, responsible for the rapid degradation of calcitonin as well as the degradation by environmental agents both during the preparation of the formulation and during the administration which is generally carried out for prolonged periods and by means of a single multi-dose dispenser.

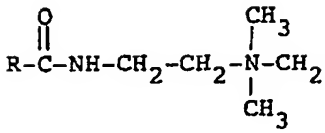
Many formulations for intra-nasal administration of calcitonin have been recently disclosed, characterized by the use of different kind of surfactants and/or absorption promoters (GB-A-2127689, EP-A-327756, EP-A-277462, EP-A-183527, EP-A-115627).

The known formulations are not however satisfactory in at least one of the following aspects: bioavailability, stability, tolerability, safety.

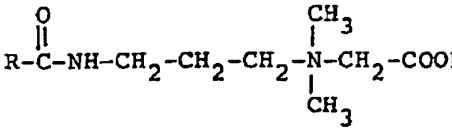
It has now been found that all the above requisites can be met by intra-nasal compositions of calcitonins containing one or more long-chain derivative of N-substituted aminoacids selected from alkylbetaines, alkylamidobetaines, carboxylated alkylimidazolidines, alkylamidopropylbetaines, alkylglycines, having the following formulas



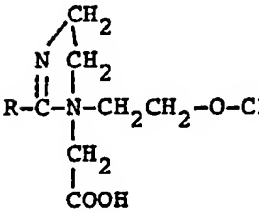
alkyl-betaine



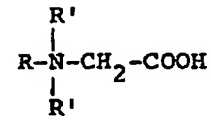
alkyl-amido-betaine



alkylamidopropyl betaine



carboxylated alkylimidazolydine



alkylglycine

wherein R and R' are alkyl residues, preferably C_{10}-C_{24} alkyl residues.

These derivatives are widely used in the pharmaceutical industry as anti-septic and detergents for external use: their use has also been proposed for rectal compositions containing calcitonin (JP-A-56118013). The technical problems connected with the rectal administration are however completely different and the favourable effects obtained in the intranasal administration are therefore surprising.

The invention refers therefore to stable pharmaceutical compositions for nasal administrations containing:

a calcitonin,

a long-chain N-substituted amino-acid derivatives and optionally preserving agents (methyl or propyl p-oxybenzoates), and

a diluent or carrier suited for the application to the nasal mucosa.

According to the invention, the term "calcitonin" comprises natural or synthetic calcitonins or similar pharmaceutically active polypeptides. Salmon, eel, porcine and human calcitonin and elcatonin, particullarly preferred, each of them being commercially available and described as far as their pharmacological activity is concered.

The amount of calcitonin in the compositions of the invention depends on the kind of selected calcitonin, on the seriousness of the diseases to be treated and on the desired administration frequency.

The long-chain N-substituted amino-acid derivative may be contained in the amount from 2 to 10 mg per ml of solution.

A preferred class of N-substituted amino-acid derivative is that of alkylamidopropylbetaines.

The methyl-p-oxybenzoate may be contained in the amount from 1.2 to 1.3 mg per ml of solution.

The propyl-p-oxybenzoate may be contained in the amount from 0.3 to 0.2 mg per ml of solution.

The liquid diluent or carrier consist of an isotonic aqueous solution buffered at pH of about 4.0.

The compositions of the invention proved to be stable towards the microbial contamination from microorganisms such as E. coli, Staph. aureus and from yeasts such as Candida albicans and Aspergillus niger.

In the stability tests, the active principle proved to be stable after 2 years at a temperature of 27° C, in nitrogen atmosphere, in glass containers.

In the stability tests in comparison with 5 units of pancreatine per ml of solution, the compositions according to the invention were stable for an observation period of 30 days at room temperature, whereas the reference composition kept during the same period in the same conditions lost about 60% of biological activity.

In the clinical test the compositions of the invention did not induce side-effects.

In the bioavailability tests carried out administering to Rhesus monkeys 50 units of calcitonin, it was shown that the compositions of the invention exhibited plasma haematic levels about 35% higher than that of a reference composition, without long-chain N-substituted amino-acids.

The invention is further illustrated by the following Examples.

EXAMPLE 1

Synthetic salmon calcitonin		1400 UI
Sodium chloride		mg 6.0
Sodium citrate $2H_2O$		mg 4.63
Citric acid H_2O		mg 4.54
Methyl p-hydroxybenzoate		mg 1.3
Propyl p-hydroxybenzoate		mg 0.2
Sodium edetate		mg 0.1
Alkylbetaine		mg 5.0
Distilled water	to	mg 1.0 ml

The methyl-p-hydroxybenzoate and propyl-p-hydroxybenzoate are dissolved in warm water. At about 20° C, under stirring, buffers, sodium edetate, sodium chloride, alkylbetaine and calcitonin are added to the solution in the order. The pH is adjusted to about 4.0 ± 0.3. The solution is filtered on Amberlite and then distributed in vials in a suited glass container of type 1, provided with a spray dispenser able to administer about 5 UI for each application.

EXAMPLE 2

Synthetic salmon calcitonin		700 UI
Sodium chloride		mg 6.0
Sodium citrate $2H_2O$		mg 4.63
Citric acid H_2O		mg 4.54
Methyl p-hydroxybenzoate		mg 1.2
Propyl p-hydroxybenzoate		mg 0.3
Sodium edetate		mg 0.1
Alkyl amino betaine		mg 7.5
Distilled water	to	mg 1 ml

The preparation process is the same as in Example 1.

EXAMPLE 3

Synthetic salmon calcitonin		1400 UI
Sodium chloride		mg 6.0
Sodium citrate $2H_2O$		mg 4.60
Citric acid H_2O		mg 4.54
Methyl p-hydroxybenzoate		mg 1.3
Propyl p-hydroxybenzoate		mg 0.2
Sodium edetate		mg 0.3
Carboxylated alkylimidazolidine		mg 2.5
Alkylglycine		mg 3.5
Distilled water	to	mg 1 ml

The preparation process is the same as in Example 1.

The preparation process is the same as in Example 1.

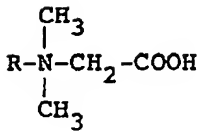
EXAMPLE 4

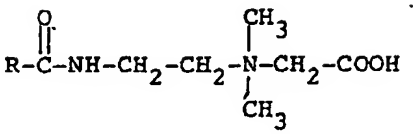
Synthetic salmon calcitonin		1400 UI
Sodium chloride		mg 6.0
Sodium citrate $2H_2O$		mg 4.60
Citric acid H_2O		mg 4.54
Methyl p-hydroxybenzoate		mg 1.3
Propyl p-hydroxybenzoate		mg 0.2
Sodium edetate		mg 0.3
Alkylamidopropyl betaine		mg 0.2
Alkylglycine		mg 3.5
Distilled water	to	mg 1 ml

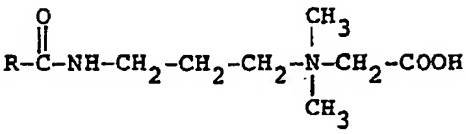
Claims

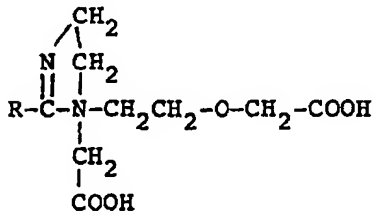
1. Pharmaceutical compositions for the intranasal administration of natural of synthetic calcitonins characterized by containing a long-chain N-subsituted amino acid.

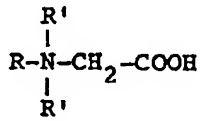
2. Pharmaceutical compositions according to claim 1 wherein the N-substituted amino acid derivative is selected from alkyl-betaines, alkylamidobetaines, carboxylated alkylimidazolidines, alkylamidopropyl-betaines, alkylglycines of formulae:











wherein R and R' are C_{10}-C_{24} alkyl residues.

3. Pharmaceutical compositions according to claim 1 or 2, wherein the N-substituted amino acid is present in concentrations from 2 to 10 mg per ml of solution.

4. Pharmaceutical compositions according to any one of the previous claims, wherein calcitonin is selected from salmon, eel, porcine, human calcitonin and elcatonin.

5. Pharmaceutical compositions according to any one of the previous claims wherein the liquid diluent or carrier consists of an isotonic aqueous solution buffered at pH 4.0 ± 0.3.

6. Pharmaceutical compositions according to any one of the previous claims characterized by containing methyl-p-hydroxybenzoates or propyl-p-hydroxybenzoates.

7. Pharmaceutical compositions according to any one of the previous claims, characterized by containing calcitonin in amount from 50 to 400 UI.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 11 7394

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	DATABASE: CHEMICAL ABSTRACTS, accession no. 81-80457D, Derwent Publications Ltd, London, GB; & JP-A-56 118 013 (TEIJIN) 16-09-1981 * Abstract *	1-2	A 61 K 9/06 A 61 K 47/18 A 61 K 37/30
A	DATABASE: CHEMICAL ABSTRACTS, accession no. 86-186015, Derwent Publicatons Ltd, London, GB; & JP-A-61 118 325 (YAMANOUCHI) 05-06-1986 * Abstract *	1-2,4-5	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	20 December 90	SCARPONI U.

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same category
A: technological background
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P: intermediate document
T: theory or principle underlying the invention

E: earlier patent document, but published on, or after the filing date
D: document cited in the application
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